REMARKS/ARGUMENTS

Claims 1, 3, 6, 7, 12, 15, and 16 are amended herein.

Claims 4, 17, and 20 are cancelled.

Claim Rejections – 35 U.S.C. § 112

Enablement

"Prodrugs"

Claims 1-21 were rejected because "prodrugs" of the claimed compounds are allegedly not enabled. Applicants have amended the claims to delete the term "prodrug." Thus, this rejection is believed to be overcome.

Applicants note, however, that they do not admit that the term "prodrug" was not enabled at the time the application was filed or that they agree with any particular assertions by the Office.

S or O in "A"

The claims were also rejected because compounds where S or O replaced a CH_2 were allegedly not enabled.[1] The specification must enable a person of ordinary skill in the art to make and use the invention without undue experimentation.[2] The Patent Office bears the burden of setting forth a reasonable explanation as to why the claims are not enabled by the specification.[3]

[1] The claim language actually says "carbon atoms may be substituted with S or O" and "CH_2 may be substituted with S or O." However, this is intended to have the same meaning as the "replaced" used by the Office.
[2] *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).
[3] *Id.* at 1561-1562.

The Office admits that compounds having O at the second carbon atom in the top chain is enabled, but alleges that the other compounds having S or O in that chain are not enabled. Applicant is not required to show that every possible embodiment is enabled, but the knowledge in the art and routine experimentation can be used to interpolate between embodiments.[4]

The Office appears to be asserting that both: 1) a person of ordinary skill in the art would not be able to make the other compounds having O or S in the top chain without undue experimentation, and 2) a person of ordinary skill would not be able find useful compounds without undue experimentation. Applicants respectfully disagree on both points.

How to Make

Going from the compounds disclosed in the specification to the other claimed compounds is textbook chemistry. The scheme below illustrates how this is the case. Step 1, at the top of the scheme illustrates how a compound such as compound 13, 25, or 59 in the specification could be modified to obtain different positions of the O or S in the top chain. First, a standard Swern oxidation or a similar reaction[5] would oxidize the hydroxyl to an aldehyde. Second, a Wittig or similar reaction[6] adds an additional carbon atom to the chain as a protected aldehyde in the form of an enol ether. Third, the aldehyde is deprotected using a standard hydrolysis.[7] Finally, this is alkylated as shown in Figures 1, 3, 4, 5, 6, 14, and 17 in the present application. Thus, a compound having O in the third position from the ring could be prepared.

[4] *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.")
[5] See Michael B. Smith and Jerry March, March's Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, New York: John Wiley & Sons, 2001, pp. 1514-1517.
[6] *Id.* at 1231-1237.
[7] *Id.* at 465-468.

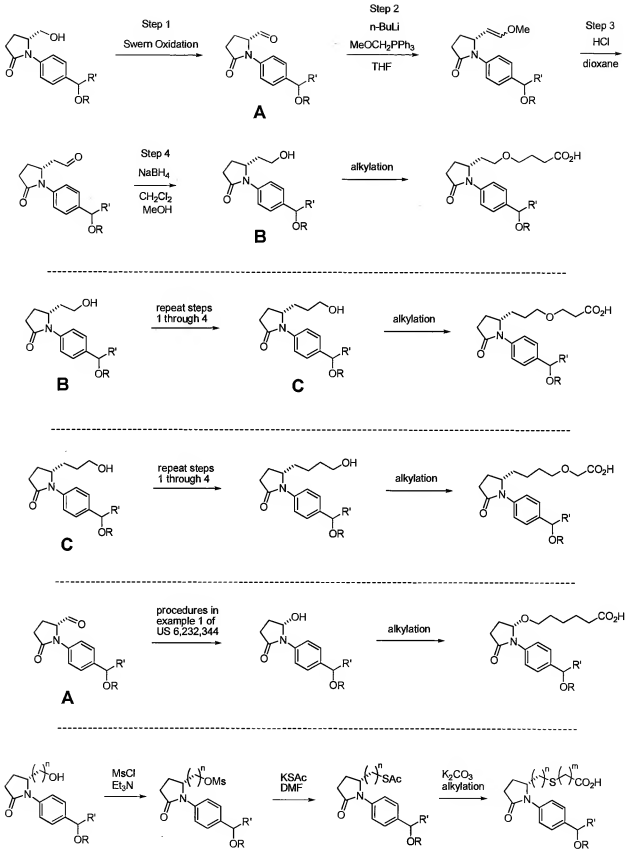
The O could be further moved down the chain to the fourth or fifth position by repeating these steps once or twice. An O in the sixth position could be obtained by an additional iteration, except that the last step would be carboxylation of an alkoxide to form the carbonate ester.[8]

US 6,232,344 provides a method that can be adapted to obtain an O directly attached to the ring.

The O could be replaced with an S by following the procedure at the bottom of the scheme. The hydroxyl is converted into a good leaving group, and a standard SN2 style reaction is then carried out using potassium thioacetate or a similar compound with a nucleophilic sulfur atom. The alkylation or carboxylation is then carried out as described above.

An additional O or S atom could be added by alkylating with a molety containing an ether or thioether functional group.

[8] *Id.* at 1184.

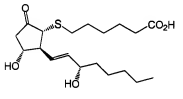

Step 1
Swern Oxidation
Step 2
n-BuLi
MeOCH2PPh3
THF
Step 3
HCl
dioxane
A
Step 4
NaBH4
CH2Cl2
MeOH
alkylation
B
repeat steps
1 through 4
C
procedures in
example 1 of
US 6,232,344
MsCl
Et3N
KSAc
DMF
K2CO3
alkylation

Thus, essentially all of the claimed compounds may be prepared using standard, textbook reactions. Applicants point out that a person of ordinary skill in the art is able to devise a scheme such as the one presented here. A primary role of the typical organic chemist is to devise routes from one compound to another using known chemistry. Indeed, this type of exercise is often an examination question for a student of organic chemistry. Therefore, a person of ordinary skill in the art could prepare the claimed compounds without undue experimentation.

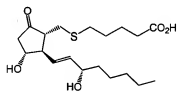
How to Use

There is an abundance of evidence that S and O can be use in place of CH_2 in any position while retaining EP2 agonist activity.

For example, in non-selective prostaglandin agonists, S can be substituted for CH_2 in any position on the chain while still maintaining significant activity.[9]



EP2 binding constant (nM) 100



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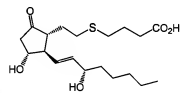

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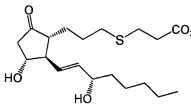
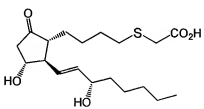


EP2 binding constant (nM) 340



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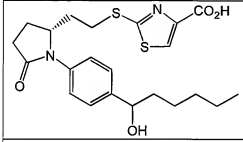
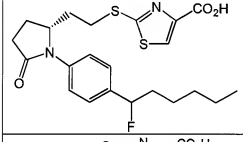
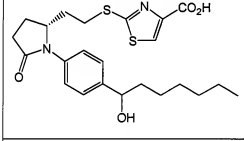
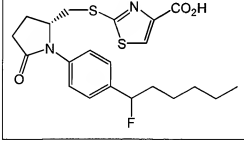
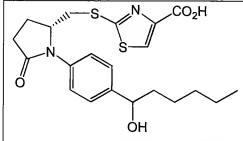
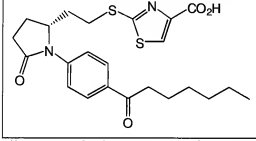
[9] Maruyama, et. al., *Bioorganic and Medicinal Chemistry*, Volume 10, Number 6, June 2002 , pp. 1743-1759(17)

Furthermore, Applicants and their associates have found other instances that compounds having S in the top chain, or O in different positions in the top chain are in fact active at the EP2 receptor. The table below shows examples taken from US Patent documents.

Structure	EP2 cAMP EC_{50} (nM)	EP2 Binding IC_{50} (nM)	Reference
	0.15	15	US Pat. App. 12/049,970
	0.09	15	
	0.23	9	US Pat. App. 12/049,970
	1.2	13	US Pat. App. 12/049,970
	0.4	9	
	117	345	US Pat. App. 12/049,970

Structure	EP2 cAMP EC_{50} (nM)	EP2 Binding IC_{50} (nM)	Reference
	120	355	US Pat. App. 12/049,970
	0.7	18	US Pat. App. 12/049,970

If two sets of values are shown for a given structures, they represent the activities of the stereoisomers. Absolute stereochemistry of these compounds was not known at the time the documents were drafted.

There is no particular position on the top chain where Applicants or any other person skilled in the art have shown that the presence of S or O makes the compound inactive at the EP2 receptor. Rather, most instances where it has been attempted, compounds with S or O in top chain are active at the EP2 receptor. Therefore, all the evidence available indicates that finding the active compounds with S or O in any position on the top chain can be done without undue experimentation. Applicants respectfully request that this rejection be removed.

"*Metabolites*"

Claims 1-21 were rejected because "metabolites" of the claimed compounds are allegedly not enabled. Applicants have amended the claims to delete the term "metabolites." Thus, this rejection is believed to be overcome.

Applicants note, however, that they do not admit that the term "metabolites" was not enabled at the time the application was filed or that they agree with any particular assertions by the Office.

Indefiniteness

"Comprising"

Claim 1 was rejected because the term "comprise" with reference to certain moieties was allegedly indefinite. Applicants have deleted the term "comprising up to 14 carbon atoms," and replaced it with the description of Y from claim 4, which does not contain the "comprising" language.

Claims 12 and 15 are amended to replace "comprising" with "of the formula."

Claim 17

Several rejections were made with respect to claim 17. Without admitting the correctness of any allegations made by the Office, Applicants have cancelled this claim to expedite prosecution.

"having"

Claims 3, 6, and 7 were also rejected for use of the phrase "having the formula." This phrase has been replaced by "of the formula." Therefore, this rejection is believed to be overcome.

"wherein 1 or 2 carbon atoms may be substituted with S or O"

Claim 1 is allegedly indefinite for the phrase "wherein 1 or 2 carbon atoms may be substituted with S or O." Applicants respectfully disagree. "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more."[10] The specification explains what this phrase means in detail and provides 52 examples. Any other species of A can be readily

[10] *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

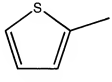
discerned by those skilled in the art. Therefore, the claims "reasonably apprise those skilled in the art" and the claims are definite.

The Office alleges that "it is unclear which of the carbon atoms in the alkyl chain will be replaced by S or O." The specification and the claims make it clear that any 1 or 2 of the $-CH_2-$ groups in the alkyl chain can be replaced by S or O. Since there are only, at most, 6 $-CH_2-$, there are a definite and discernable number of substitutions that may be made. Therefore, the claim is definite.

"interthienylene,"

The Office alleges that "interthienylene" is not commonly known in the art or defined in the specification. Applicants point out that the specification (p. 8, line 20-22) states "[i]nterarylene or heterointerarylene refers to an aryl ring or ring system or a heteroaryl ring or ring system which connects two other parts of a molecule, i.e. the two parts are bonded to the ring in two distinct ring positions."

A person of ordinary skill knows that thienyl is a species of "heteroaryl." Thus, the person of ordinary skill would understand that "interthienylene" refers to thienyl which connects two other parts of the molecule, The term "thienyl" is well known in the art. For example, if one enters the terms "thienylmethane," into the most recent versions of ChemDraw, the structures below is produced.



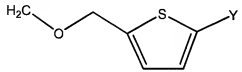
thienylmethane

Furthermore, Applicants have provided ample explanation, including both structural and named examples, to clarify the meaning of "interthienylene." For the

convenience of the Office, Applicants include here examples of "interthienylene" from the specification.

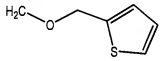
Examples of "interthienylene"  from the specification.

Page 9



(line 13)

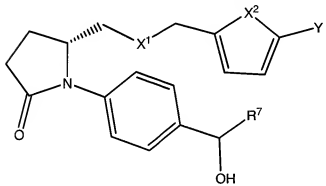
Page 10



("where Y is attached to the aromatic or heteroaromatic ring." line 6)

Page 16

Other compounds comprise



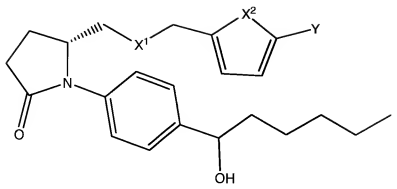
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof,

wherein X^1 and X^2 are independently CH, O, or S; and

R^7 is linear alkyl comprising from 3 to 7 carbon atoms. (lines 4-8)

Page 16-17 (Spanning paragraph)

Other compounds comprise



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof, wherein X^1 and X^2 are independently CH, O, or S.

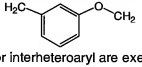
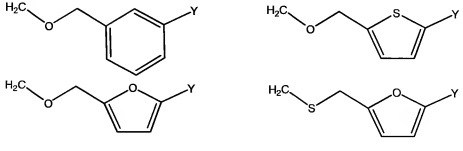
Examples from the Table (pp 68-77)

Example numbers: 4, 9,12, 13, 14, 15, 16, 17, 18, 19, 20, 23, 24, 27, 28, 34, 35, 36, 39, and 40.

Therefore, a person of ordinary skill in the art is reasonably apprised of the meaning of "interthienylene," and the term is not indefinite.

"interaryl" and "interheteroaryl"

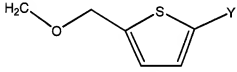
The allegedly indefinite language of claims 12 and 15 reads: "G is 1,3-interaryl or interheteroaryl." The specification (p. 9, lines 10-18) contains the following:

> In another embodiment, Ar is 1,3 interaryl or interheteroaryl, where Ar attached at the 1 and 3 positions, such as when A has the structure shown below.
>
> 
>
>
> Other examples of 1,3 interaryl or interheteroaryl are exemplified in the following examples of A-Y.
>
> 
>

Thus, from the specification, it is clear that "1,3 interaryl or interheteroaryl" refers to an aryl or heteroaryl ring where Y and the chain portion of A are attached to carbon atoms that are separated by a single ring atom, such as in the structures above. Thus, a person of ordinary skill are reasonably apprised of the meaning of "1,3 interaryl or interheteroaryl" in claims 12 and 15. Therefore, the rejection should be removed.

"*Interthienyl*"

Claim 16 has been amended to refer to claim 15. In the portion of the specification explaining "1,3 interaryl or interheteroaryl," the following structure is present.



As explained above, a person of ordinary skill recognizes that one name for this ring is "thienyl." Thus, a person reading claim 15, which refers to 1,3 interaryl, would realize that interthienyl in claim 16 refers to the thienyl ring as depicted in the structure above, or a structure with the S atom in a different position (although not necessarily with the same chain). Thus, this term is also not indefinite.

Claim Rejections – 35 U.S.C. § 101

The rejected claim 20 is cancelled. Thus, this rejection is now moot.

Double Patenting

The claims are provisionally rejected based on the judicially created double patenting doctrine. As pointed out by the Office, this doctrine is "grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees." (Office Action, p. 16). The present claims and the two patent applications used as the basis for this rejection do not offend these basic policy rationales underlying this doctrine because the asserted applications could not be used to extend the "right to exclude," nor could they cause harassment by multiple assignees.

The claimed compounds are not the "same invention" as those claimed in Serial Numbers 11/778,800 and 11/747,490. There is no compound that would infringe the present claims that would also infringe a claim in either of these other applications. Neither do the other applications describe a prodrug, metabolite, salt, or some other biologically equivalent form of the any compound in the present application. Thus, there is no way that the Applicant could use these later applications to extend the exclusivity of any embodiment protected by the claims.

Neither is there any possibility that the '800 or '490 applications could cause harassment by multiple assignees. If the Applicants were to assign these applications to another party, there is no compound that a person could make that would infringe both the claims in the present application and the claims in either the '800 or '490 application. Thus, multiple parties could not harass an infringer of the claims of the present application.

Therefore, the double patenting rejection is improper.

In light of the amendments and arguments made herein, Applicants respectfully request that the claims be allowed.

No fee is believed due in connection with this communication. However, if applicant is in error please charge Deposit Account 01-0885 for any fees related to this response.

Respectfully submitted,

Dated: May 21, 2008

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Enclosures:

1. Maruyama, et. al., Bioorganic and Medicinal Chemistry, Volume 10, Number 6, June 2002 , pp. 1743-1759(17).
2. Michael B. Smith and Jerry March, March's Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, New York: John Wiley & Sons, 2001, pp. 465-468, 1184, 1231-1237,1514-1517.
3. Serial No. 12/049,970